

Journal Watch

Reviewed by SY Cheng 鄭秀儀 (coordinator), LY Chan 陳來源, SCK Ho 何正綱, LS Ku 顧立誠

Topical tacrolimus therapy for vitiligo: therapeutic responses and skin messenger RNA expression of proinflammatory cytokines

Grimes PE, Morris R, Avaniss-Aghajani E, Soriano T, Meraz M, Metzger A.
J Am Acad Dermatol 2004;51:52-61.

This was a study to evaluate the efficacy and safety of topical tacrolimus 0.1% ointment in the treatment of generalised vitiligo. The pre- and post-treatment cytokine expressions in the depigmented and normal skin of patients were compared with controls.

Twenty-three patients were recruited. Nineteen of them completed the study and were compared with 15 control subjects. Patients were treated with topical tacrolimus twice daily for 24 weeks. Three-millimeter punch biopsy specimens were taken from the depigmented, non-sun-exposed skin and adjacent uninvolved skin of patients at baseline and at 24 weeks. Cytokine expressions were determined by real-time quantitative polymerase chain reaction and compared to controls.

Varying degree of repigmentation occurred in 17 patients (89%). Thirteen patients (68%) had more than 75% repigmentation of face and/or neck lesions. The overall disease severity scores at 24 week were significantly reduced ($p=0.021$). At baseline, vitiligo patients had significantly increase in the expression of IFN- γ , TNF- α and IL-10 in involved and uninvolved skin. After treatment, TNF- α expression significantly decreased ($p<0.001$) while there was no change in the IFN- γ and IL-10 expression. The alteration in the cytokine

expression may play a role in the pathogenesis of vitiligo. The suppression of TNF- α expression after treatment with topical tacrolimus may be associated with repigmentation of vitiligo. This study was supported through a research grant from Fujisawa Healthcare.

A multicenter, randomised, double-blind, placebo-controlled study of efficacy and safety of 3 doses of botulinum toxin A in the treatment of glabellar lines

Ascher B, Zakine B, Kestemont P, Baspeyras M, Bougara A, Santini J.
J Am Acad Dermatol 2004;51:223-33.

This was a multicenter, randomised, double-blind study to determine the efficacy and safety of three doses of botulinum toxin A in the treatment of glabellar lines. A total of 119 patients with moderate to severe glabellar lines at rest were recruited. The patients were randomised to receive intramuscular injection of 25, 50, or 75U of botulinum toxin A (Dysport, Ipsen) or placebo, divided into five glabellar injection sites. The primary outcome was measured by independent experts' evaluation of blinded standardised photographs taken one month after treatment. The secondary outcome measures included physician evaluations and patient assessments during a 6-month follow-up period.

At one month after injection, the primary outcome measures were significantly greater for the three treatment groups as compared to placebo

(44.8% for 25U and 50U, $p=0.015$; 55.2% for 75U, $p=0.005$; and 6.7% for placebo). Both the investigator (25U: 72.4%; 50U: 93.1%; 75U: 75.9%) and patient evaluations (25U: 65.5%; 50U: 86.2%; 75U: 75.8%) suggested that 50U was the optimal dose. The treatment was well tolerated and no blepharoptosis was reported. However, it was noted that both the subjective evaluation by physicians and patients generated higher scores than the objective evaluation by the blinded independent experts.

The study concluded that botulinum toxin A is effective and safe in the treatment of glabellar lines. The authors also emphasised that the units of this botulinum toxin A preparations are not interchangeable with any other preparations. This study was supported by Beaufour Ipsen Pharma SAS.

Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases

Bianchi L, Orlandi A, Campione E, Angeloni C, Costanzo A, Spagnoli LG, et al.
Br J Dermatol 2004;151:148-56.

Tazarotene has been proposed to treat selected cases of basal cell carcinomas (BCCs) such as those in low risk areas, surgically inaccessible sites and patients with multiple neoplasms.

This study evaluated 109 patients (74 men and 35 women; age 41-91 years; mean age 69.6 years) with 154 BCCs. There were 108 superficial BCCs and 46 nodular BCCs, with size ranging from 0.2 to 2 cm in diameter. Tazarotene 0.1% gel was applied every evening for 24 weeks. Partial regression is defined as clinical reduction in both diameter and thickness by $>50\%$, and healing is defined as complete regression. BCCs regressed by $<50\%$ were regarded as unresponsive.

Response was assessed by both clinical, dermoscopic and histological examination. The overall responsive rate, partial regression rate and healing rate were 70.8%, 40.3% and 30.5% respectively. The respective rates for superficial BCCs and nodular BCCs were 89.8%, 25%, 64.8% and 67.4%, 39.1%, 28.3%. The response rates were 87.5%, 78% and 58% for BCCs at the extremities, head and neck, and the trunk and back respectively. Among the unresponsive BCCs, 69% were of the keratotic histological subtype. Adverse reactions like erythema and slight superficial erosions were observed in 23.4% of the patients, with pruritus and burning observed in 22.9% of the patients, mainly during the first week. No relapse was noted among healed BCCs at three years follow-up. This study concluded that topical tazarotene is an alternative treatment in superficial and nodular BCCs.

Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis

Kyllönen H, Remitz A, Mandelin JM, Elg P, Reitamo S.
Br J Dermatol 2004;150:1174-81.

This study aimed at evaluating long-term (one year) changes in collagen synthesis and skin thickness in patients applying intermittent topical tacrolimus monotherapy. Adult patients older than 18 years with moderate to severe atopic dermatitis were recruited. Fifty-six of them received 0.1% tacrolimus ointment twice daily to active lesions for one year. Other therapies were prohibited. An exception was the rescue therapy used for severe exacerbations after the first half of the study, for which a course of topical or systemic corticosteroid for a single period within three months for a maximum of two weeks was permitted. Another 36 patients with moderate to severe atopic dermatitis receiving moderately

potent conventional topical corticosteroid and 27 healthy subjects were recruited as controls. The skin thickness, using ultrasound measurements, and pro-collagen propeptide I and III levels were measured for all the patients and healthy controls at baseline, and at 12 months for all the atopic dermatitis patients.

It was found that the skin thickness and pro-collagen propeptide I and III levels for the tacrolimus group was significantly increased after treatment when compared with the corticosteroid group. The pro-collagen propeptide I and III levels for the tacrolimus treated group were similar to healthy controls. It was concluded that long term tacrolimus in the treatment of atopic dermatitis is non-atrophogenic and reverse corticosteroid-induced skin atrophy. It is not known, however, whether tacrolimus has any direct effect on collagen synthesis or the increase is due to cessation of topical corticosteroid usage.

Bioavailability of betamethasone dipropionate when combined with calcipotriol

Traulsen J.

Int J Dermatol 2004;43:611-7.

Betamethasone dipropionate and calcipotriol are commonly used medications for the treatment of psoriasis. Due to incompatibility of formulations they cannot be applied simultaneously together. The new once-daily formulation combining calcipotriol (50 ug/g) and betamethasone dipropionate (0.5 mg/g) is more convenient to use and may improve patient compliance. Using the vasoconstrictor assay, this study looked into the bioavailability of betamethasone dipropionate when combined with calcipotriol. It comprised of two phases, a pilot and a pivotal phase. The pilot phase determined the optimal dose-duration of the unmixed reference betamethasone dipropionate ointment for use in the pivotal phase, which compared the biological activity of the

reference ointment and the test combination ointment.

Twelve healthy subjects aged 18-45 years were recruited in the pilot phase to apply 10 ul of betamethasone dipropionate reference ointment to eight 1.5 cm sites on each forearm under occlusion for 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0 hours. Vasoconstriction as manifested by skin blanching was evaluated by a chromameter and by visual inspection. The basic biological activity of betamethasone dipropionate was determined by the half-maximal response (ED_{50}), the $0.5 \times ED_{50}$ and the $2.0 \times ED_{50}$. Another 32 healthy subjects were recruited in pivotal phase to apply the test combination ointment at the dose-duration corresponding to the ED_{50} obtained in the pilot phase to two sites per forearm.

The two formulations were found to bear equivalent biological activity in terms of the vasoconstrictive responses analysed using both an objective chromametric measurement of skin blanching and a visual evaluation. It was thus concluded that the steroid component of the combined formulation is not adversely affected by the presence of calcipotriol.

A double-blind randomised trial of 5% ascorbic acid vs 4% hydroquinone in melasma

Espinal-Perez LE, Moncada B, Castanedo-Cazares JP.

Int J Dermatol 2004;43:604-7.

This study compared the safety and efficacy of topical 5% L-ascorbic acid and 4% hydroquinone in the treatment of melasma. Sixteen women with skin type IV and V, age ranged from 23 to 43 years (mean, 36) with idiopathic bilateral symmetrical facial melasma were recruited in this double-blinded trial.

They were randomised and instructed to apply

on the left or right face ascorbic acid or hydroquinone water-oil emulsion at night for 16 weeks. All patients were requested to apply UVA and UVB sunscreen every three hours each morning. Patients were assessed every four weeks using digital photography, colorimetry, regular colour slides and subjective patient evaluation. All side effects were registered.

There were 93% and 62.5% of patients showing more than 50% subjective improvement with hydroquinone and ascorbic acid respectively. The subjective improvement on the hydroquinone side was statistically significant ($p < 0.05$). There was, however, no difference in improvement between the two sides when analysed by colorimetry, implying that the melanin component decreased similarly in the two treatments. Improvement with hydroquinone was evident at the first month, whereas that for ascorbic acid was noted at the third month. Irritation was reported in 68.75% and 6.25% of the patients using hydroquinone and ascorbic acid respectively. The response rates did not correlate with the type and duration of melasma. The study concluded that ascorbic acid has a beneficial effect on melasma, and its tolerability makes it good for long-term maintenance treatment.

Evaluation of sexual function with an international index of erectile function in subjects taking finasteride for androgenetic alopecia

Tosti A, Pazzaglia M, Soli M, Rossi A, Rebora A, Atzori L, et al.
Arch Dermatol 2004;140:857-8.

The effect of finasteride on sexual function was evaluated in this study. Patients taking finasteride 1 mg/day for androgenetic alopecia were evaluated before and at four to six months after beginning treatment by the International Index of Erectile Function (IIEF-5) questionnaire. This was a self-assessment questionnaire consisting of five

items: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall sexual satisfaction. All subjects were followed-up as outpatients.

A total of 186 patients (range of age 19-43 years, mean 28.3 years) were studied. The findings were as follows: erectile function: baseline 27.14 ± 2.49 ; at 4-6 months 27.53 ± 2.26 ; orgasmic function: baseline 9.04 ± 1.38 , at 4-6 months 9.15 ± 1.26 ; sexual desire: baseline 8.07 ± 1.30 , at 4-6 months 8.13 ± 1.35 ; intercourse satisfaction: baseline 11.42 ± 1.79 , at 4-6 months 11.78 ± 1.89 and overall sexual satisfaction: baseline 8.32 ± 1.41 , at 4-6 months 8.51 ± 1.28 . None of these changes were significant. The authors concluded that sexual side effects from finasteride were less common than previously reported. However, as the follow-up period was relatively short, the long-term side-effects were still unclear.

Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease

Renaud-Vilmer C, Cavelier-Balloy B, Porcher R, Dubertret L.
Arch Dermatol 2004;140:709-12.

The long-term effect of topical steroids on vulvar lichen sclerosus (VLS) was evaluated in this study. Eighty-three women with histologically confirmed VLS were treated with 0.05% clobetasol propionate ointment once daily for three months and then three times per week until complete remission (CR). CR was defined both clinically (absence of clinical signs of VLS) and histologically.

The median follow-up time was 4.7 years (range 2 months to 19 years) and the mean patient age was 59.4 years (range 30-92 years). CR occurred in 45 (54%) patients and cumulative incidence rate of CR was 32% at three years and 58% at six

years. Symptoms resolved within three months of treatment in all cases. There was a significant effect of age on resolution ($p < 0.001$). The incidences of CR at three years were 72% in patients under 50 years old; 23% in those between 50 and 70 years old and 0% in those over 70 years of age. The incidence of relapse was 50% at 16 months (95% confidence interval: 30-64%) and 84% at four years (95% confidence interval 57-94%). These findings were not affected by age.

Eight cases (9.6%) of squamous cell carcinoma (SCC) were observed (median age 68.6 years). Six of these occurred before treatment was started and the remainder occurred in irregularly treated cases. The authors concluded that VLS in women older than 70 years, might be improved by topical steroids, but CR could not be achieved. In younger patients, remission could be achieved with long-term topical steroids although relapses were common. These findings suggested a protective effect of potent topical steroid from malignant change but the number of SCC was too small.

Does treatment of vulvar lichen sclerosis influence its prognosis?

Cooper SM, Gao XH, Powell JJ, Wojnarowska F. *Arch Dermatol* 2004;140:702-6.

The clinical course and response to topical steroids in 327 patients (74 girls, 253 women) with a confirmed diagnosis of vulvar lichen sclerosis were analyzed in this descriptive cohort study. The mean age of onset of symptoms was 5.4 years for girls and 55.1 years in women. Childhood onset of disease was defined as onset of symptoms before menarche and a definite diagnosis at or before the age of 16 years. For all patients, information was collected by direct interview, clinical examination and review of case notes. Mean age at diagnosis was 7.6 years for girls and 60 years for women with an average delay in diagnosis of 4.6 years. Mean duration of follow-up after diagnosis was 66 months (range 4-350

months). The most common symptoms in women were anogenital pruritus (89%), and soreness (69%). Girls presented more frequently with urinary or bowel symptoms and purpura than women. Vulval scarring occurred significantly less commonly in girls. Cases diagnosed within two years were associated with less scarring ($p < 0.008$).

An ultrapotent topical steroid (0.05% clobetasol propionate ointment) was used by 31 (50%) girls and 208 (89%) women. Other steroid preparation was used by the rest. Symptoms were improved in 244 (96%) patients of which 168 (66%) were symptom free, 76 (30%) had a partial response and 11 (4%) responded poorly. There was total resolution of clinical signs in eight (22%) girls and 50 (23%) women. Partial resolution of clinical signs occurred in 24 (67%) girls and 149 (69%) women. Minor resolution was seen in four (11%) girls and 14 (6%) women. Six cases of squamous cell carcinoma were detected (mean age at diagnosis 63.8 years, range 39-82 years). There was a greater delay in diagnosis (15.3 vs 4.4 years) in these cases. However, there were too few cases for any conclusions to be made.

The authors concluded that ultrapotent topical steroids might improve symptoms in vulvar lichen sclerosis with resolution of clinical signs and early treatment might prevent scarring.

Lichen striatus: clinical and laboratory features of 115 children

Patrizi A, Neri I, Fiorentini C, Bonci A, Ricci G. *Pediatr Dermatol* 2004;21:197-204.

The clinical features and response to treatment in 115 children (37 boys, 78 girls, age at diagnosis ranged from one month to 13 years, mean age four years five months) with lichen striatus were evaluated. The lesions most commonly started in the winter months (46 cases) and the family history was negative in all but two pairs of siblings. Nail

lichen striatus was seen in only three boys while the majority of cases (89 cases) presented with typical lesions. Hypopigmented lesions were seen in 18 cases. Lesions followed Blaschko lines in most cases, though lesions in seven cases followed the axial lines of Sherrington. The limbs were the most commonly affected sites. The lesions always followed Blaschko lines when the trunk or face was affected.

There was an association with atopy in 70 cases (60.86%). There was no significant difference between atopics and non-atopics, in terms of mean age of onset or disease duration. Treatment with topical steroids did not affect the duration of disease. In 105 patients, there was spontaneous resolution (follow-up time two months to ten years). The mean duration of disease was six months and hypochromic sequelae occurred in 30 (28.57%) cases. Relapses were seen in five children and a prolonged course was seen in one case only. While an aetiological factor (such as prodromic symptoms of a viral infection and previous skin trauma) was suspected in five cases, the cause remained unknown in the majority of cases.

The authors concluded that an association between lichen striatus and atopy might be found. In cases that follow the axial lines, they suggested that this may be an illusory phenomenon where several Blaschko lines are affected to appear as a single band.

Risk factors for incomplete excision of basal cell carcinomas

Bogdanov-Berezovsky A, Cohen AD, Glesinger R, Cagnano E, Krieger Y, Rosenberg L. *Acta Derm Venereol* 2004;84:44-7.

This was a cross-sectional study of 1278 patients who had a primary excision of basal cell carcinomas (BCCs) in an ambulatory and hospital plastic surgery department. The medical files and

the pathologic reports were reviewed to assess the adequacy of the excisions. The risk factors for incomplete excision of BCCs, defined as the presence of tumour cells at the surgical margins of the lesion, were identified.

BCCs were incompletely excised in 159 of 1478 primary excision (10.8%). Incomplete excision was significantly associated with tumour location in the eyelids (OR 3.64, 95% CI 1.96-6.71), ears (OR 2.51, 95% CI 1.25-4.94), nasolabial folds (OR 2.26, 95% CI 0.99-5.04) and nose (OR 1.88, 95% CI 1.30-2.71). An inverse association was found for tumour location in the upper limbs (OR 0.44, 95% CI 0.21-0.90), back (OR 0.12, 95% CI 0.02-0.48) or chest (OR 0.09, 95% CI 0.00-0.57). Baso-squamous differentiation was also associated with incomplete excision of BCCs ($p=0.03$). Other factors including gender, age, operation setting, clinical appearance or diameter of the lesion were not associated with incomplete excision.

The authors recommended special surgical measures for BCCs located at eyelids, ears, nasolabial folds and nose, in order to avoid inadequate excision of the tumours at these sites.

Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis

Luger TA, Lahfa M, Fölster-Holst R, Gulliver WP, Allen R, Molloy S, et al.

J Dermatol Treat 2004;15:169-78.

In this randomised, double-blind, multi-centre study, 658 adult patients with moderate to severe atopic dermatitis were recruited. The patients were randomised to apply 1% pimecrolimus cream or topical corticosteroids (1% triamcinolone acetonide cream for trunk and limbs, and 1% hydrocortisone acetate cream for face, neck and intertriginous area) twice daily until complete

clearance of lesions or for up to one year. Their long-term safety and tolerability were compared over the study period.

In patients with severe (over 30% body surface area involved) atopic dermatitis, skin infections occurred less frequently in the pimecrolimus group (15.4%) than in the corticosteroid group (29.7%) (95% CI of the treatment difference: -25.3% to -3.4%). The efficacy at all time points, as indicated by the median overall Eczema Area and Severity Index, showed that topical corticosteroid was better than topical pimecrolimus ($p \leq 0.006$). However, the investigator assessment scores did not show any difference between the two groups

at the end of the study. Forty-two percent of pimecrolimus-treated patients were maintained for one year without topical corticosteroids. Local application site burning reaction occurred in 25.9% of patients on pimecrolimus and 10.9% on topical corticosteroids. There were no serious or clinically significant systemic adverse events.

The authors concluded that topical pimecrolimus has a favourable safety profile for use up to one year. It may play an important role in the long-term control as a maintenance measure while topical corticosteroid can be restricted for short-term acute flares. This study was funded by a research grant from Novartis Pharma AG.

Answers to Dermato-venereological Quiz on pages 223

1. The most likely clinical diagnosis is prurigo pigmentosa, as the clinical features are distinct and typical. Other differential diagnoses include Nekam's disease, reticular erythematous mucinosis, lichen planus pigmentosus, eczema, confluent and reticulate papillomatosis of Gougerot-Carteaud.
2. Prurigo pigmentosa is a chronic inflammatory dermatosis characterised by pruritic, reddish, papulo-vesicular lesions and gross reticular pigmentation that occurs mainly on the back and healed with post-inflammatory hyperpigmentation. Majority of the cases were described in Japan. The cause and pathogenesis have yet to be determined. Histologically, it is characterised by a lichenoid tissue reaction with intraepidermal vesiculation, spongiosis and ballooning. Subepidermal vesiculation with vacuolar alteration at the dermo-epidermal junction is also noted. Direct immunofluorescence was negative.
3. Prurigo pigmentosa has been associated with helicobacter pylori infection, diabetic ketoacidosis, ketosis related to anorexia nervosa, malnutrition and contact allergens such as chrome.
4. Minocycline and dapsons are effective and both inhibit migration and function of neutrophils. Other options include doxycycline, clarithromycin and roxithromycin. Possible associated clinical conditions should be managed accordingly.